Iron-deficiency anemia

Iron-deficiency anemia, also spelled **iron-deficiency anaemia**, is defined as a decrease in the amount of red blood cells (RBCs) or hemoglobin in the blood due to not enough iron.[1][2] When anemia comes on slowly the symptoms are often vague and may include: feeling tired, weakness, shortness of breath or a poor ability to exercise. Anemia that comes on quickly often has greater symptoms which may include: confusion, feeling like one is going to pass out, and increased thirst. There needs to be significant anemia before a person becomes noticeably pale. There may be additional symptoms depending on the underlying cause.[3]

It is caused by insufficient dietary intake and absorption of iron, or iron loss from bleeding. Bleeding can be from a range of sources such as the intestinal, uterine or urinary tract. The most significant cause of iron-deficiency anemia in developing world children is parasitic worms: hookworms, whipworms, and roundworms. Worms cause intestinal bleeding, which is not always noticeable in faeces, and is especially damaging to growing children.[4] Malaria, hookworms and vitamin A deficiency contribute to anemia during pregnancy in most underdeveloped countries.[5] In women over 50 years old, the most common cause of iron-deficiency anemia is chronic gastrointestinal bleeding from nonparasitic causes, such as gastric ulcers, duodenal ulcers or gastrointestinal cancer.

Iron deficiency causes approximately half of all anemia cases worldwide, and affects women more often than men. Iron-deficiency anemia affects nearly 1 billion.[6] In 2013 anemia due to iron deficiency resulted in about 183,000 deaths – down from 213,000 deaths in 1990.[7]

1 Signs and symptoms

Iron-deficiency anemia is characterized by the sign of pallor (reduced oxyhemoglobin in skin or mucous membranes), and the symptoms of fatigue, lightheadedness, and weakness. None of the symptoms (or any of the others below) are sensitive or specific. Pallor of mucous membranes (primarily the conjunctiva) in children indicates anemia with best correlation to the actual disease, but in a large study was found to be only 28% sensitive and 87% specific (with high predictive value) in distinguishing children with anemia [hemoglobin (Hb) <11.0 g/dl] and 49% sensitive and 79% specific in distinguishing severe anemia (Hb < 7.0 g/dl).[8] Thus, this sign is reasonably predictive when present, but not helpful when

absent, as only one-third to one-half of children who are anemic (depending on severity) will show pallor. Irondeficiency must be diagnosed by laboratory testing.

Because iron deficiency tends to develop slowly, adaptation occurs and the disease often goes unrecognized for some time, even years; patients often adapt to the systemic effects that anaemia causes. In severe cases, dyspnea (trouble breathing) can occur. Unusual obsessive food cravings, known as pica, may develop. Pagophagia or pica for ice has been suggested to be specific, but is actually neither a specific or sensitive symptom, and is not helpful in diagnosis. When present, it may (or may not) disappear with correction of iron-deficiency anemia.

Other symptoms and signs of iron-deficiency anemia include:

- Anxietand obsessionsy often resulting in OCD-type compulsions
- Irritability or a low feeling
- Angina
- Constipation

- Sleepiness/Hypersomnia
- Tinnitus
- Mouth ulcers
- Palpitations
- Hair loss
- Fainting or feeling faint
- Depression
- Breathlessness
- Twitching muscles
- Pale yellow skin
- Tingling, numbness, or burning sensations
- Missed menstrual cycle
- Slow social development
- Glossitis (inflammation or infection of the tongue)
- Angularmouth's corners)cheilitis (inflammatory lesions at the
- Koilonychia (spoon-shaped nails) or nails that are weak or brittle
- Poor appetite
- Pruritus (itchiness)
- Dysphagia due to formation of esophageal webs (Plummer-Vinson syndrome)
- Insomnia
- Restless legs syndrome[9]

1.1 Infant development

Iron-deficiency anemia for infants in their earlier stages of development may have greater consequences than it does for adults. An infant made severely iron-deficient during its earlier life cannot recover to normal iron levels even with iron therapy. In contrast, iron deficiency during later stages of development can be compensated with sufficient iron supplements. Iron-deficiency anemia affects neurological development by decreasing learning ability, altering motor functions, and permanently reducing the number of dopamine receptors and serotonin levels. Iron deficiency during development can lead to reduced myelination of the spinal cord, as well as a change in myelin composition. Additionally, iron-deficiency anemia has a negative effect on physical growth. Growth

hormone secretion is related to serum transferrin levels, suggesting a positive correlation between iron-transferrin levels and an increase in height and weight. This is also linked to pica, as it can be a cause.

2 Cause

A diagnosis of iron-deficiency anemia then requires further investigation as to its cause. It can be caused by increased iron demand / loss or decreased iron intake,[10] and can occur in both children and adults. The cause of chronic blood loss should all be considered, according to the patient's sex, age, and history, and anaemia without an attributable underlying cause is sufficient for an urgent referral to exclude underlying malignancy. In babies and adolescents, rapid growth may outpace dietary intake of iron, and result in deficiency without disease or grossly abnormal diet.[10] In women of childbearing age, heavy or long menstrual periods can also cause mild irondeficiency anemia.

2.1 Parasitosis

The leading cause of iron deficiency worldwide is infestation with parasitic worms (helminths such as tapeworms, flukes, and roundworms). The World Health Organization estimates that "approximately two billion people are

infected with soil-transmitted helminths worldwide."[11] Parasitic worms cause both inflammation and chronic blood loss.

2.2 Blood loss

Blood contains iron within red blood cells, so blood loss leads to a loss of iron. There are several common causes of blood loss: Women with menorrhagia (heavy periods) are at risk of iron-deficiency anemia because they are at higher-than-normal risk of losing a larger amount blood during menstruation than is replaced in their diet. Slow, chronic blood loss within the body — such as from a peptic ulcer, angiodysplasia, a colon polyp or gastrointestinal cancer — can cause iron-deficiency anemia. Gastrointestinal bleeding can result from regular use of some groups of medication, such as NSAIDs e.g. aspirin, anticoagulants such as clopidogrel and warfarin, although these are required in some patients, especially those with states causing thrombophilia.

2.3 Diet

The body normally gets the iron it requires from foods. If a person consumes too little iron, or iron that is poorly absorbed (non-heme iron), they can become iron deficient over time. Examples of iron-rich foods include meat, eggs, leafy green vegetables and iron-fortified foods. For proper growth and development, infants and children need iron from their diet, too.[12] A high intake of cow's milk is associated with an increased risk of iron deficiency anaemia.[13] Other risk factors for iron deficiency low meat intake and low intake of iron-fortified products.[13]

2.4 Iron absorption

Iron from food is absorbed into the bloodstream in the small intestine, especially the duodenum and proximal ileum. Many intestinal disorders can reduce the body's ability to absorb iron. There are different mechanisms that may be present.

In cases where there has been a reduction in surface area of the bowel, such as in celiac disease, inflammatory bowel disease or post surgical resection, the body can absorb iron, but there is simply insufficient surface area.

If there is insufficient production of hydrochloric acid in the stomach, hypochlorhydria/achlorhydria (often due to chronic H. pylori infections or long-term proton pump inhibitor therapy) Ferrous and Ferric iron salts will precipitate out of solution in the bowel which are poorly absorbed.

In cases where systemic inflammation is present, iron will be absorbed into enterocytes, but due to the reduction in basolateral ferroportin molecules which allow iron to pass into the systemic circulation, iron is trapped in the enterocytes and is lost from the body when the enterocytes are sloughed off.

Depending on the disease state, one or more mechanisms may occur.

2.5 Pregnancy

Without iron supplementation, iron deficiency anemia occurs in many pregnant women because their iron stores need to serve their own increased blood volume as well as be a source of hemoglobin for the growing fetus, and for placental development.[12]

Other less common causes are intravascular hemolysis and hemoglobinuria.

3 Mechanism

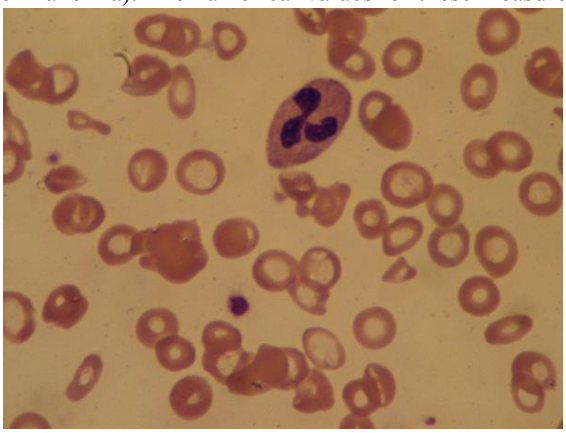
Anemia is one result of significant iron deficiency. When the body has sufficient iron to meet its needs (functional iron), the remainder is stored for later use in all cells, but mostly in the bone marrow, liver, and spleen. These stores are called ferritin complexes and are part of the human (and other animals) iron metabolism systems. Ferritin complexes in humans carry about 4500 iron atoms and form into 24 protein subunits of two different types.[14]

4 Diagnosis

Anemia may be diagnosed from symptoms and signs, but when it is mild, it may not be diagnosed from mild nonspecific symptoms. Pica, an abnormal craving for dirt, ice, or other "odd" foods occurs variably in iron and zinc deficiency, but is neither sensitive or specific to the problem, so is of little diagnostic help.

Anemia is often first shown by routine blood tests, which generally include a complete blood count (CBC) which is performed by an instrument which gives an output as a series of index numbers. A sufficiently low hemoglobin (Hb) by definition makes the diagnosis of anemia, and a low hematocrit value is also characteristic of anemia. Further studies will be undertaken to determine the anemia's cause. If the anemia is due to iron deficiency, one of the first abnormal values to be noted on a CBC, as the body's iron stores begin to be depleted, will be a high red blood cell distribution width (RDW), reflecting an increased variability in the size of red blood cells (RBCs). In the course of slowly depleted iron status, an increasing RDW normally appears even before anemia appears.

A low mean corpuscular volume (MCV) often appears next during the course of body iron depletion. It corresponds to a high number of abnormally small red blood cells. A low MCV, a low mean corpuscular hemoglobin and/or mean corpuscular hemoglobin concentration, and the appearance of the RBCs on visual examination of a peripheral blood smear narrows the problem to a microcytic anemia (literally, a "small red blood cell" anemia). The numerical values for these measures are all calculated by modern laboratory equipment.



Blood smear of a patient with iron-deficiency anemia at 40X enhancement

The blood smear of a patient with iron deficiency shows many hypochromic (pale and relatively colorless) and rather small RBCs, and may also show poikilocytosis (variation in shape) and anisocytosis (variation in size). With more severe iron-deficiency anemia, the peripheral blood smear may show target cells, hypochromic pencilshaped cells, and occasionally small numbers of nucleated red blood cells.[15] Very commonly, the platelet count is slightly above the high limit of normal in iron deficiency anemia (this is mild thrombocytosis). This effect was classically postulated to be due to high erythropoietin levels in the body as a result of anemia, cross-reacting to activate thrombopoietin receptors in the precursor cells that make platelets; however, this process has not been corroborated. Such slightly increased platelet counts present no danger, but remain valuable as an indicator even if their origin is not yet known.

The diagnosis of iron-deficiency anemia will be suggested by appropriate history (e.g., anemia in a menstruating woman or an athlete engaged in long-distance running), the presence of occult blood (i.e., hidden blood) in the stool, and often by other history.[16] For example, known celiac disease can cause malabsorption of iron. A travel history to areas in which hookworms and whipworms are endemic may be helpful in guiding certain stool tests for parasites or their eggs.

Body-store iron deficiency is diagnosed by diagnostic tests, such as a low serum ferritin, a low serum iron level, an elevated serum transferrin and a high total iron binding capacity. A low serum ferritin is the most sensitive lab test for iron deficiency anemia. However, serum ferritin can be elevated by any type of chronic inflammation and so is not always a reliable test of iron status if it is within normal limits (i.e., this test is meaningful if abnormally low, but less meaningful if normal).

Serum iron levels (i.e. iron not part of the hemoglobin in red cells) may be measured directly in the blood, but these levels increase immediately with iron supplementation (the patient must stop supplements for 24 hours), and pure blood-serum iron concentration in any case is not as sensitive as a combination of total serum iron, along with a measure of the serum iron-binding protein levels (TIBC). The ratio of serum iron to TIBC (called iron saturation or transferrin saturation index or percent) is the most specific indicator of iron deficiency, when it is sufficiently low. The iron saturation (or transferrin saturation) of < 5% almost always indicates iron deficiency, while levels from 5% to 10% make the diagnosis of iron deficiency possible but not definitive. Saturations over 12% (taken alone) make the diagnosis unlikely. Normal saturations are usually slightly lower for women (>12%) than for men (>15%), but this may indicate simply an overall slightly poorer iron status for women in the “normal” population.

Iron-deficiency anemia and thalassemia minor present with many of the same lab results. It is very important not to treat a patient with thalassemia with an iron supplement, as this can lead to hemochromatosis (accumulation of iron in various organs, especially the liver). A hemoglobin electrophoresis provides useful evidence for distinguishing these two conditions, along with iron studies.

4.1 Gold standard

Conventionally, a definitive diagnosis requires a demonstration of depleted body iron stores obtained by bone marrow aspiration, with the marrow stained for iron.[17][18] Because this is invasive and painful, while a clinical trial of iron supplementation is inexpensive and not traumatic, patients are often treated based on clinical history and serum ferritin levels without a bone marrow biopsy. Furthermore, a study published April 2009[19] questions the value of stainable bone marrow iron following parenteral iron therapy.

5 Treatment

See also: Lucky iron fish

Anemia is sometimes treatable, but certain types of anemia may be lifelong. If the cause is dietary iron deficiency, eating more iron-rich foods, such as beans, lentils or red meat, or taking iron supplements, usually with iron(II)

NaFerredetate EDTA, will usually correct the anemia. Alternatively, intravenous iron can be administered.

Recent research suggests the replacement dose of iron, at least in the elderly with iron deficiency, may be as little as 15 mg per day of elemental iron. An experiment done in a group of 130 anemia patients showed a 98% increase in iron count when using an iron supplement with an average of 100 mg of iron. Women who develop iron deficiency anemia in mid-pregnancy can be effectively treated with low doses of iron (20–40 mg per day). The lower dose is effective and produces fewer gastrointestinal complaints. The body apparently adapts to oral iron supplementation, so iron is often effectively started at a comparatively low dose, then slowly increased.

Anemia during pregnancy can cause fetal distress; women may undergo caesarean section as treatment.[20]

The difference between iron intake and iron absorption, also known as bioavailability, can be great. Scientific studies indicate iron absorption problems are worsened when iron is taken in conjunction with milk, tea, coffee and other substances. A number of methods that can help mitigate this, including:

- Fortification with ascorbic acid increases bioavailability in both presence and absence of inhibiting substances, but is subject to deterioration from moisture or heat. Ascorbic acid fortification is usually limited to sealed, dried foods, but individuals can easily take ascorbic acid with a basic iron supplement for the same benefits. The primary benefit over ascorbic acid is durability and shelf life, particularly for products like milk, which undergo heat treatment.
- Microencapsulation with lecithin binds and protects the iron particles from the action of inhibiting substances.
- Using an iron amino acid chelate, such as NaFeEDTA, similarly binds and protects the iron particles. A study by the hematology unit of the University of Chile indicated chelated iron (ferrous bis-glycine chelate) can work with ascorbic acid to achieve even higher absorption levels. • Separating intake of iron and inhibiting substances by a few hours
- Using nondairy milk (such as soy, rice, or almond milk) or goats' milk instead of cows' milk • Gluten-free diets can resolve some instances of irondeficiency anemia, if it is a result of celiac disease. • Heme iron, found only in animal foods, such as meat, fish and poultry, is more easily absorbed than nonheme iron, found in plant foods and

  supplements.[21][22]

Iron bioavailability comparisons require stringent controls, because the largest factor affecting bioavailability is the subject's existing iron level. Informal studies on bioavailability usually do not take this factor into account, so exaggerated claims from health supplement companies based on this sort of evidence should be ignored. Scientific studies are still in progress to determine which approaches yield the best results and the lowest costs.

If anemia does not respond to oral treatments, it may be necessary to administer iron parenterally using a drip or hemodialysis. Parenteral iron involves risks of fever, chills, backache, myalgia, dizziness, syncope, rash, and with some preparations, anaphylactic shock. The total incidence of adverse events is much lower than that with oral tablets (where the dose needs to be reduced or treatment stopped in over 40% of subjects) and blood transfusions.

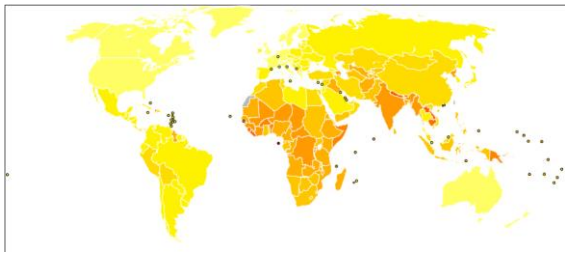
A follow-up blood test is essential to demonstrate whether the treatment has been effective; it can be undertaken after two to four weeks. With oral iron, this usually requires a delay of three months for tablets to have a significant effect.

5.1 Iron supplementation and infection risk

Because one of the functions of elevated ferritin (an acute phase reaction protein) in acute infections is thought to be to sequester iron from bacteria, it is generally thought that Parenteral iron supplementation (which circumvents this mechanism) should be avoided in patients who have active bacterial infections bacteraemia. Replacement of iron stores is seldom such an emergency situation that it cannot wait for such infections to be treated, although occasionally cases will arise where this is not possible, such as chronic osteomyelitis.

Iron deficiency protects against infection by creating an unfavorable environment for bacterial growth. Some studies have found iron supplementation can lead to an increase in infectious disease morbidity in areas where bacterial infections or where malaria are common. For example, children receiving iron-enriched foods have demonstrated an increased rate in diarrhea overall and enteropathogen shedding. Nevertheless, while iron deficiency might lessen infections by certain pathogenic diseases, it also leads to a reduction in resistance to other strains of viral or bacterial infections, such as *Salmonella typhimurium* or *Entamoeba histolytica*. Overall, it is sometimes difficult to decide whether iron supplementation will be beneficial or harmful to an individual in an environment prone to many infectious diseases; however, this is a different question than the question of supplementation in individuals who are already ill with a bacterial infection.

6 Epidemiology



Disability-adjusted life year for iron-deficiency anemia per 100,000 inhabitants in 2004.[23] no data less than 50 50-100 100-150 150-200 200-250 250-300 300-350 350-400 400-450 450-500 500-1000 more than 1000

A moderate degree of iron-deficiency anemia affected approximately 610 million people worldwide or 8.8% of the population.[6] It is slightly more common in female (9.9%) than males (7.8%).[6] Mild iron deficiency anemia affects another 375 million.[6]